

REMARKS/ARGUMENTS***The Present Invention***

The present invention is directed to a process for providing a human with a therapeutic protein.

The Pending Claims

Claims 15-22 and 24-33 are pending.

The Office Action

The Office Action rejects claims 15-29 under 35 USC 251 and 37 CFR 1.658 as allegedly corresponding to the count lost in Interference 104,712. The Office further objects to claims 15-29 under 37 CFR 1.633 and MPEP 2363.03 on the grounds of estoppel. Furthermore, the Office rejects claim 23 as allegedly containing new matter and rejects claims 15-29 as allegedly non-enabled. Reconsideration of the rejections and objection to the claims is hereby requested.

The Amendments to the Claims

Claim 23 has been canceled. Claims 15 and 27 have been amended to recite "autologous" in front of "human cells" and "human B-lymphocytes," respectively, which is supported by the instant specification at, for example, column 13, line 1. Claims 17-21 and 25 have been amended to correct claim dependencies. Claims 16-22, 24-26, 28, and 29 have been amended to insert a comma before "wherein." Claims 30-33 have been added and are supported by the specification at, for instance, column 5, lines 22-26. No new matter has been added by way of these amendments.

Discussion of the Rejection under 35 USC 251 and 37 CFR 1.658

The Office rejects claims 15-29 under 35 USC 251 and 37 CFR 1.658 as allegedly corresponding to the count lost in Interference 104,712. Specifically, the Office contends that the judgment of the Interference (Paper No. 91) states that: "Anderson is not entitled to a patent containing claims 1-14 of Anderson's 5,399,346 patent, which corresponds to count 1." However, the judgment should have read "claims 1-6, 8-11, 13, and 14" in lieu of "claims 1-

14." See Erratum (Paper No. 92; copy of which is attached hereto). Accordingly, claims 7 and 12 of the '346 patent are not included in the claims to which Anderson is not entitled. Further, although claims 7 and 12 were part of the count, there was no determination as to the priority of these claims. The judgment only deemed claims 1-6, 8-11, 13, and 14 as unpatentable. Claims 7 and 12 were not deemed as unpatentable, however, (see last sentence of first full paragraph on page 54 of Paper No. 88). In view of the foregoing and in light of the fact that the pending claims of the instant application are based on claims 7 and 12 of the '346 patent, the rejection of the pending claims under 35 USC 251 and 37 CFR 1.658 should be withdrawn.

Discussion of the Rejection under 37 CFR 1.633 and MPEP 2363.03

The Office further objects to claims 15-29 under 37 CFR 1.633 and MPEP 2363.03 on the grounds of estoppel. This rejection is traversed for the reason set forth below.

MPEP 2363.03, under the paragraph entitled "Estoppel" states: "As stated in 37 CFR 1.658 (c), a losing party who could have properly moved under 37 CFR 1.633 or 1.634, but failed to do so, is estopped from taking subsequent action in the USPTO which is inconsistent with the party's failure to properly move." The Office specifically alleges that applicants did not attempt to separate the subject matter of patent claims 7, 10, and 12 from the count. In Anderson Preliminary Motion 5 (Paper No. 28), applicants sought to designate claims 2-7 and portions of claims 8-14 of the '346 patent as not corresponding to the count. Thus, applicants did, in fact, properly move under 37 CFR 1.633 or 1.634. Since claims 15-29 of the instant application are based on claims 7 and 12 of the '346 patent, claims 15-29 are not subject to estoppel.

Discussion of the New Matter Rejection

The Office rejects claim 23 is under 35 USC 251 as allegedly based upon new matter. Claim 23 has been canceled herein. Thus, the rejection is moot.

Discussion of the Enablement Rejection

Claims 15-29 are rejected under Section 112, first paragraph, as allegedly non-enabled. The Office specifically contends that the specification does not provide enabling disclosure for "the therapeutic expression of any protein, including any cytokine, by

administering any type of human cell, whether B-lymphocytes or other types of primary cells, to a human." The Office further contends that "the specification fails to provide any specific guidance for transducing B-lymphocytes, or provide any guidance or evidence regarding the treatment of any disease by administering transduced B-lymphocytes expressing a therapeutic protein." This rejection is traversed for the reasons set forth below.

As a first matter, applicants point out that claims 7 and 12 of the '346 patent, which are the claims upon which the instantly pending claims are based, were found to be enabled by the specification and was thus deemed patentable at least once by the Office. Thus, the enablement rejection for these reasons alone appears to be improper.

The rejection is further traversed because the claims are not directed to methods of treating a disease, and, therefore, the specification is not required to provide any guidance or evidence regarding the treatment of any disease.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive. *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, the nature of the invention is a process for providing a human with a therapeutic protein. The process comprises introducing autologous human cells into a human, said autologous human cells having been treated *in vitro* to insert therein a DNA segment encoding a therapeutic protein, said autologous human cells expressing *in vivo* in said human a therapeutically effective amount of said therapeutic protein. The breadth of claims 15-26 and 30-33 is limited to autologous human cells as the cells that provide the therapeutic protein and to therapeutic proteins that are cytokines other than TNF. The

breadth of claims 27-29 is limited to autologous B-lymphocytes as the autologous human cells which provide the therapeutic protein. All claims are limited to autologous human cells (or autologous human B-lymphocytes) expressing *in vivo* in said human a therapeutically effective amount of said therapeutic protein.

The instant specification provides ample amounts of direction and guidance for practicing the inventive process and further provides working examples. For instance, the specification at column 11, line 62 through column 12, line 8 teaches a method of constructing a vector containing a gene encoding a therapeutic protein. Also, the specification at column 13, line 62 to column 14, line 22, and at column 15, lines 1-17, teaches how to transduce a T-lymphocyte. The specification at column 15, line 43 through column 16, line 13 teaches a method of culturing and transducing tumor cells. Methods of harvesting cells for introduction into a human and methods of introducing cells into a human are taught by the instant specification at, for example, column 14, lines 23-52 and column 17, lines 9-24. The specification furthermore teaches the special precautions and additional steps necessary for carrying out the inventive process in humans. For instance, the specification teaches to test for the absence of the viral envelope gene, for the absence of provirus, and for sterility and cell viability (see column 12, lines 33-62, for example).

The instant specification further demonstrates how the TNF protocol described in Example 4 can be adapted to other cells and other genes. For instance, the protocol of Example 6 is similar to the TNF protocol, in that autologous cells are transduced with a retroviral vector encoding a therapeutic protein and then the transduced cells are administered to the human from which the autologous cells came. Unlike the TNF protocol, Example 6 describes the isolation and culturing of primary tumor cells, the transduction of tumor cells, instead of T-lymphocytes, and the injection of the transduced tumor cells for the production of TIL. Also, Example 7 is the same as the gene therapy protocol described in Example 6, except that the retroviral vector encodes a cytokine other than TNF, namely, IL-2. Therefore, one of ordinary skill in the art recognizes the adaptability of the gene therapy protocol to other autologous cells and other genes encoding therapeutic proteins.

The Office contends that the specification fails to provide any specific guidance for transducing B-lymphocytes. As stated above, sufficient guidance for carrying out the present inventive method is found in the specification. It appears that the Office requires that the specification teach how to carry out every possible embodiment of the present inventive

method. "An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*, 654 F.2d 103, 105, 210 UAPQ 689, 691 (CCPA 1981). "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." *In re Gay*, 309F.2d 769, 774, 50 CCPA 725, 733, 135 USPQ 311, 316 (CCPA 1962).

Further, as stated in paragraph 3 of the Declaration of Dr. Steven A. Rosenberg (the Rosenberg Declaration; attached hereto), the methods of transducing T-lymphocytes taught in the instant specification can be employed for cells other than T-lymphocytes, e.g., B-lymphocytes. There is nothing in the disclosed protocol which makes it specific for T-lymphocytes. For example, the protocol does not include the use of a vector that has a T-lymphocyte-specific promoter. Also, the protocol does not include the use of a retroviral vector which targets a T-lymphocyte-specific molecule for infection. Further, since the protocol comprises administering the retroviral vector to a mixed population of cells, it is likely that cells other than the T-lymphocytes of the mixed population are transduced during the protocol. Therefore, the specification teaches a protocol that can be used with cells other than T-lymphocytes, including B-lymphocytes.

The Office argues at length that the state of the art of gene therapy at the time of filing the instant application was such that a process of providing a human with a therapeutic protein other than ADA and TNF using cells other than T lymphocytes was unpredictable.

On the contrary, as stated in paragraph 4 of the Rosenberg Declaration, the TNF protocol served as the basis for other gene therapy clinical protocols using different genes and different cells. For instance, this protocol served as the basis for the protocols used or being used in the gene therapy clinical trials for the following genes: IL-2, IL-15, IL-21, IFN- γ , a T cell receptor. Also, this protocol is the basis for the protocol currently used in a clinical trial with CD34 $^{+}$ stem cells. As stated in paragraph 6 of the Rosenberg Declaration, data that indicates that the protocols successfully provided a human with the gene product has been obtained by Dr. Rosenberg's laboratory from each of the gene therapy trials of IL-2 and a T cell receptor. Thus, one of ordinary skill in the art, given the benefit of the TNF protocol of the instant specification, was enabled to make and use the claimed process with therapeutic proteins other than ADA and TNF and with cells other than T lymphocytes.

Further, the state of the art was not so unpredictable that one of ordinary skill in the art was unable to devise other gene therapy protocols with genes other than the TNF and

ADA genes. As stated in the Declaration of W. French Anderson (the Anderson Declaration; attached hereto), which was originally submitted to the Office during the prosecution of U.S. Application No. 07/904,662, thirty-seven gene therapy protocols involving a variety of genes were approved shortly after the ADA protocol of the instant specification was approved by the Recombinant DNA Advisory Committee (RAC). Such protocols included the expression of IL-2, the LDL receptor, thymidine kinase, HLA-B7, IL-4, IIV-gp120, p53, antisense-RAS, CF, GM-CSF, IFN-gamma, MDR, Rev, anti-IGF-1, and a ribozyme (paragraph 4 of the Anderson Declaration). It is even stated therein that such approved protocols involved a variety of delivery means, such as retroviral vectors, adenovirus vectors, liposomes for delivery of plasmid DNA, and viral producer cells. According to the Anderson Declaration, such protocols encompassed both *ex vivo* and *in situ* transduction of human cells.

Therefore, one of ordinary skill in the art having the benefit of the protocols of the instant application possessed the knowledge and skill to devise reasonably effective gene therapy protocols with other genes without undue experimentation. In view of the foregoing, the instantly pending claims are enabled by the instant specification.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention *In re Wright*, 999F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by the claim is not adequately enabled by the disclosure). MPEP 2164.04

The Office argues that the state of the art is so unpredictable and quotes many skilled artisans casting doubt on the whole concept of gene therapy and cites the many problems of gene therapy. However, the Office does not provide evidence supporting that one of ordinary skill in the art could not use *the disclosed protocols* for other genes or with other cells. The burden to provide such evidence is on the Office. It is not enough for the Examiner to merely argue that certain aspects of the field of gene therapy are unpredictable and problematic.

The Office further contends that the specification does not provide any data that supports that the disclosed protocols correlated with a therapeutic effect on the patient. There is no *per se* requirement for such data. In fact, MPEP 2164.05 states that an applicant can provide a declaration after the filing date which demonstrates that the claimed invention works. Such a declaration is provided herein (see the Rosenberg Declaration, paragraph 5).

As stated in paragraph 5 of the Rosenberg Declaration, the TNF protocol was successful in providing a human patient with a therapeutically effective amount of TNF. This patient has survived for more than 10 years due to the TNF gene therapy. Also, data demonstrating that the ADA protocol was successful in providing a human with therapeutically effective amounts of ADA are disclosed in Blaese et al., *Science* 270: 475-480 (1995), Mullen et al., *Human Gene Therapy* 7: 1123-1129 (1996); and Onodera et al., *Blood* 91: 30-36 (1998); copies of which are attached hereto. In view of the foregoing, the disclosed protocols do, in fact, provide therapeutically effective amounts of a therapeutic protein to a human.

The Office further contends that the claims broadly read on allogeneic human cells. Claims 15 and 27 have been amended to limit the cells to "autologous human cells" and "autologous human B-lymphocytes," respectively. Support for the term "autologous" is found in the instant application at, for instance, column 13, line 1. Thus, the rejection on these grounds is moot.

The Office further alleges that the specification provides no specific guidance as to the level of expression of any of these proteins which correlates with a therapeutic effect on any disease or condition, and does not provide any evidence that any type of human cell transduced with the disclosed retroviral vectors, or any other type of vector, would be capable of stably expressing such a therapeutic level of each protein once transplanted into a human host.

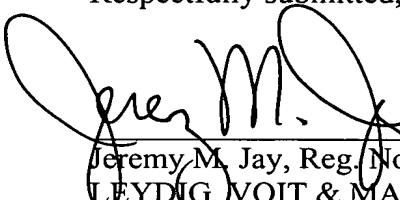
As discussed above and as stated in paragraph 6 of the Rosenberg Declaration, the TNF protocol was the basis for both a gene therapy protocol for expression of a T cell receptor and a gene therapy protocol for expression of IL-2. Dr. Rosenberg's laboratory has obtained data from both of these clinical trials indicating that therapeutically effective amounts of the T cell receptor and of IL-2 were provided to the humans in the clinical trials. One patient in the T cell receptor gene therapy trial has survived for more than ten years, due to the expression of the T cell receptor. In view of the foregoing, one of ordinary skill in the art could reasonably predict that the protocols described in the instant application could be used to achieve therapeutically effective amounts of a therapeutic gene other than TNF and ADA.

In view of the foregoing, the pending claims of the instant invention are enabled by the specification. Applicants, therefore, request that the rejection be withdrawn.

Conclusion

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



Jeremy M. Jay, Reg. No. 33,587
LEYDIG, VOIT & MAXER
700 Thirteenth Street, N.W., Suite 300
Washington, DC 20005-3960
(202) 737-6770 (telephone)
(202) 737-6776 (facsimile)

Date: August 16, 2005

M:\clients\nih\amd\219974 am1.doc